UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,632	02/16/2001	Jin-Soo Kim	12279-002001	3563

26161 7590 05/30/2006

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,632	KIM ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,86,87,89-99,107,112 and 117-119* is/are pending in the application.

4a) Of the above claim(s) *24-31,34,35,87,94,99,107,112 and 117-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,32,33,63,86,89-93 and 95-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/13/2006 has been entered.

Receipt is acknowledged of an amendment, filed 3/13/2006, in which claims 36-85, 88, 100-106, 108-111 and 113-116 were canceled, and claims 1, 16, 21 and 95-98 were amended. Currently, claims 1-35, 86, 87, 89-99, 107, 112 and 117-119 are pending.

Election/Restrictions

Claims 24-31, 34-35, 87, 94, 99, 107, 112, and 117-119 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/9/02 and 10/30/03.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 5-9, 13, 21, 86, 89-91, 93 and 95-97 are rejected under 35 U.S.C. 102(e) as being anticipated by Joung et al (US Patent Application Publication No. 2003/0044787 A1; see the entire reference).

Regarding claims 1, 21, 86, 93, 95 and 96, Joung et al teach assays to identify zinc finger domains that recognize a target site on a DNA, comprising (1) providing cells containing a reporter gene construct, comprising a reporter gene operably linked to a promoter, (2) providing a plurality of hybrid nucleic acids, each of which encodes a composite DNA binding domain of an assembly of DNA binding motifs from various transcription factors, and an activation domain, (3) introducing the chimeric nucleic acids into the cells, (4) allowing the chimeric protein to be expressed, and (4) identifying a cell that contains a chimeric nucleic acid encoding a protein that binds the target DNA sequence and activates transcription of at least one reporter gene (e.g. paragraphs [0020], [0120]-[0151], [0437], [0521]-[0523], [0536], [0549]-[0554] and [0552]).

Regarding claim 2, Joung et al teach the use of eukaryotic host cells, including yeast and mammalian cells (e.g. paragraphs [0568]-[0570]).

Regarding claim 5, 6 and 13, Joung et al teach the use of a selectable marker as a reporter gene (e.g. paragraphs [0126] and [0132]). Joung et al teach the use of the yeast HIS3 gene as a reporter gene (e.g. paragraph [0133]).

Regarding claims 7 and 97, Joung et al teach the use of a second reporter gene, including one that gives rise to a detectable signal such as color, fluorescence or luminescence, such as LacZ or GFP (e.g. paragraphs [0138], [0144] and [0145]).

Regarding claim 8, Joung et al teach the use of DNA binding domains comprising zinc fingers (e.g. paragraph [0151], [0536] and [0552]).

Regarding claim 9, Joung et al teach the use of one or two zinc finger domains for low affinity binding for use as one component of the composite DNA binding domain (e.g. paragraph [0552].

Regarding claims 89 and 90, Joung et al teach that the suitable DNA binding domains, including zinc finger domains, for the composite DNA binding domain may be obtained from human proteins (e.g. paragraph [0548] and [0552]).

Regarding claim 91, Joung et al teach that positive reporter gene expression for a fluorescent marker such as EGFP occurs when the reporter gene is expressed at a 2-fold more than control cells (e.g. paragraph [0674]).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a certified copy of the foreign priority papers has not been provided, and a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 13-22, 32-33, 86, 88-93, and 95-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (U.S. Patent No. 6,242,568 B1, cited in a prior action; see the entire reference) in view of Cheng et al (U.S. Patent No. 5,869,250, cited in a prior action, Applicant reference EA; see the entire reference). This is a new rejection necessitated by the applicant's amendment to the claims (limiting each test zinc finger domain to a zinc finger domain from a naturally occurring protein) filed 3/13/2006.

Barbas teaches a method for identifying a modulating polypeptide derived from a zinc-finger nucleotide binding polypeptide that binds to a zinc-finger-nucleotide binding motif of interest comprising incubating components, comprising a nucleotide sequence encoding the putative modulating protein (which comprises a trans-modulating protein sequence) operably linked to a first inducible promoter and a reporter gene operably linked to a second inducible promoter and a zinc-finger nucleotide binding motif, wherein the incubating is carried out under conditions sufficient to allow the components to interact, and measuring the effect of the putative modulating protein on the expression of the reporter gene, such as beta-galactosidase (e.g. columns 25-27). Incubation of the components may be in vitro or in vivo, in vivo including prokaryotic or eukaryotic systems. Whether or not the putative modulating protein binds to the zinc finger-nucleotide binding motif which is operably linked the second inducible promoter, and

affects its activity is measured by the expression of the reporter gene. Other commonly used assays to assess the function from a promoter, including CAT assay will be known to those of skill in the art (e.g. paragraph bridging columns 26-27). Both prokaryotic and eukaryotic systems can be utilized (e.g. column 27). The invention is useful for the identification of a novel zinc finger-nucleotide binding polypeptide derivative or variant and the nucleotide sequence encoding the polypeptide. The zinc finger-nucleotide binding polypeptide derivative may be derived or produced from a wild type zinc finger protein by expansion where the zinc finger modules from more than one wild type polypeptide are assembled to form "hybrid" zinc finger nucleotide binding polypeptides (e.g. column 7, lines 20-40). Zinc finger proteins of the invention can be manipulated to recognize and bind an extended target sequence, such as using from 2 to 20 zinc fingers (column 28). Libraries of hybrid nucleic acids each of which encodes a polypeptide comprising a DNA binding region that recognizes part of the total zinc finger nucleotide binding motif (which reads on the claimed "recruitment site") or a binding site for a Jun/Fos leucine zipper and zinc fingers, having conserved domain boundaries made by PCR from a template in cDNA, are made, expressed and assayed for binding to a modified binding site for each individual zinc finger using phagemid display/affinity selection (e.g. columns 9-10, 14-15, and 25-27).

Barbas does not specifically teach use of the in vivo method of identifying a modulating polypeptide taught by the reference (using the reporter expression system), applied to identifying hybrid nucleic acids that encode a polypeptide comprising one test zinc finger domain (which potentially binds to a modified part of the zinc finger-nucleotide binding motif) and the two other zinc finger domains constant (binds to the unmodified part of the zinc finger-nucleotide binding

motif). This reference also does not specifically teach the use of *S. cerevisiae* yeast cells for the assay, use of a selectable marker, such as URA3, HIS3, etc as the reporter gene. This reference does not teach the fusion of cells to introduce the reporter gene and artificial nucleic acid into the same cell.

Cheng et al teach a method for identifying biologically significant peptide-DNA binding interactions and sequence-specific DNA binding peptides in vivo using combinatorial oligonucleotide libraries, preferably in yeast (e.g. abstract). The method comprises providing host cells containing selectable markers, providing a recombinant vector containing a coding sequence encoding a protein that activates gene expression when in proximity to a target DNA sequence, the DNA sequence comprising a regulatory element, and the recombinant vector containing a selectable marker, inserting into the coding sequence in a plurality of recombinant vectors a random oligonucleotide so that the resulting vectors encode a plurality of different fusion proteins, each containing a protein that activates gene expression, and a peptide encoded by the random oligonucleotide, providing a reporter vector, the reporter vector comprising a reporter gene, the DNA regulatory element, and a selectable marker, co-transfecting the host cells with the DNA vectors and the reporter vectors, and then culturing the transfected host cells in a selective medium, so that only those host cells containing a vector DNA expressing a fusion protein that contains a peptide capable of sequence-specific binding to the target DNA sequence grow therein (e.g. column 2). The transfection may be accomplished by any suitable means, including methods employing liposomes, microinjection, cell fusion, DEAE-dextran, calcium phosphate precipitation, electroporation, microparticle bombardment, conjugation into a complex internalized into a cell, and other techniques know to those skilled in the art (e.g. column 8, lines

5-33). Reporter genes for use in the method are taught as including HIS3, LEU2, TRP1, CAT, luciferase, and GFP (e.g. column 7, lines 43-62). For HIS3, LEU2, and TRP1, the genome of the cells used lack a functional copy of the gene and the cells are maintained in a medium prepared without the metabolite. Yeast, such as *S. cerevisiae*, are taught as host cells for the method (e.g. column 8). Cheng et al teach the method using yeast combinatorial libraries consisting of the Gal4 activation domain, a partial DNA binding domain that is unchanged (using two zinc fingers), and a synthetic oligo library which encode a test peptide for the rest of the DNA binding domain, which is changed (which corresponds to the target site) (column 14). Binding of the three finger positive control (which binds to the unaltered full DNA sequence) was compared to a two finger negative control polypeptide was compared, showing at least a 100-fold difference (e.g. column 16). This showed that binding of all three zinc fingers were required to specifically recognize the entire DNA sequence. Cheng et al teach that the previous way of using phage display combinatorial library techniques and affinity selection to identify peptide-nucleotide interactions fails to provide a method of identifying biologically significant peptide-DNA binding events, and the method taught by Cheng et al has the advantage of identifying biologically significant peptide-DNA binding interactions (e.g. column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the screening of zinc finger polypeptides taught by Barbas, by substituting the phagemid display/affinity selection with the in vivo expression method taught by Cheng et al because Cheng et al teach that it is within the ordinary skill in the art to use the in vivo expression method to identify peptide-DNA binding interactions, and Cheng et al specifically teach the use of this method to identify a peptide from a randomized library which binds to an

altered target sequence in a polypeptide that also comprises two unaltered zinc fingers that bind the rest of the DNA sequence which is also not altered. The assays of Cheng and Barbas serve the same purpose of identifying DNA-protein interactions. Barbas also makes obvious this substitution because Barbas teaches that it is within the ordinary skill in the art to use the same type of in vivo expression method for identifying a modulating polypeptide.

It would have been obvious to make the substitution for the expected benefit of identifying the altered zinc finger peptides which bind to the altered target sites in a biologically significant fashion and thus result in making a nucleic acid that encodes a polypeptide that has a biologically significant peptide-DNA binding interaction with the altered nucleotide sequence. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Regarding the use of three zinc finger domains for binding to the recruitment site, it would have been obvious to use one or more additional zinc fingers that bind to the unaltered nucleotide sequence because Barbas teaches that it is within the ordinary skill in the art to use the method taught by the reference to bind extended regions, using from 2 to 20 zinc fingers.

Regarding the use of amplifying a plurality of nucleic acids each of which encodes a test zinc finger domain using an oligonucleotide primer that anneals to a nucleic acid encoding a conserved domain boundary, it would have been obvious to do so because Barbas teaches the use of PCR to make mutagenized test zinc finger encoding DNA, with conserved boundaries in making the expression vectors.

Regarding the use of natural human zinc fingers as test zinc finger domains, it would have been obvious to do so because Barbas teaches that different zinc fingers can be used in the methods, including from proteins that are natural human proteins.

Regarding identifying a cell that expresses the reporter gene at least 10 fold higher than a given level, it would have been obvious to do so because the positive versus negative controls taught by Cheng et al showed at least a hundred fold difference and thus the method of Cheng et al would score as a positive result that level of difference of expression.

Regarding fusing cells to obtain a cell comprising a reporter and an artificial nucleic acid, it would have been obvious to do so because the method requires the introduction of the nucleic acid molecules into a host cell and Cheng et al teach the use of any method known to one of skill in the art, including cell fusion.

Claims 12 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas in view of Cheng et al as applied to claims 1-11, 13-22, 32-33, 86, 88-93, and 95-98 above, and further in view of Eisenberg et al (U.S. patent No. 6,453,242 B1 cited in a prior action, Applicant reference FB; see the entire reference). This is a new rejection necessitated by the applicant's amendment to the claims (limiting each test zinc finger domain to a zinc finger domain from a naturally occurring protein) filed 3/13/2006.

Barbas and Cheng et al are taught above and applied as before.

Barbas and Cheng et al do not specifically teach identifying a candidate zinc finger domain amino acid sequence in a sequence database, providing the candidate sequence, and using the sequence to construct a hybrid nucleic acid for inclusion in the hybrid nucleic acids.

Eisenberg et al teach a method of designing a zinc finger protein comprising using a database and computer program to identify candidate zinc finger domains corresponding to first, second, and/or third fingers which bind a selected target sequence based upon a scoring system (e.g. columns 4-6). Rational criteria for design include application of substitution rules and computerized algorithms for processing information in a database storing information of existing zinc finger protein designs and binding data (e.g. column 7). A zinc finger protein binding to a novel sequence for which a precharacterized zinc finger protein does not exist can be made using this approach (e.g. column 17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method made from the combined teachings of Barbas and Cheng et al by using as a candidate zinc finger one of the zinc fingers identified in a database as binding a particular sequence as taught by Eisenberg et al because Barbas teaches that it is within the ordinary skill in the art to use any zinc finger in the method taught by the references and Eisenberg et al teach that it is within the ordinary skill in the art to use a zinc finger protein from a database as the basis for the design of a zinc finger protein that binds to a novel sequence.

One would have been motivated to do so for the expected benefit of having a much larger and versatile starting point from which to design and test zinc finger proteins, a database which has many different zinc fingers, having many different binding specificities, which can be used as the basis for binding to an altered sequence. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - - 35 USC § 103

Applicant's arguments filed 3/13/2006 have been fully considered but they are not persuasive.

The response essentially asserts that Applicants are unaware of which section of the Barbas patent teaches the use of natural human proteins and asserts that the teachings of Barbas emphasize the use of zinc finger domains from naturally occurring proteins as a starting point for mutagenesis. This is not found persuasive because the Barbas patent teaches the use of zinc finger-nucleotide binding polypeptide derivatives that are produced from wild type zinc finger proteins by (1) truncation or expansion, or (2) mutagenesis (e.g. column 7, lines 20-40). As stated in the Barbas patent, "Expansion refers to a zinc finger polypeptide to which additional zinc finger modules have been added. For example, TFIIIA may be extended to 12 fingers by adding 3 zinc finger domains. In addition, a truncated zinc finger-nucleotide binding polypeptide may include zinc finger modules from more than one wild type polynucleotide, thus resulting in a "hybrid" zinc finger-nucleotide binding polypeptide." See column 7, lines 33-40. See also Example 12.

The response asserts that the basis for the rejection of claim 98 could not be found in the references. The rejection points to column 8, lines 5-33 as the basis for the rejection of this claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE [illegible] PH.D.
PRIMARY [illegible] ER